REMARKS

Claims 49-50, 54-55, 72 and 92-93 are pending in the subject application. By this amendment, Claims 55, 92 and 93 have been amended. Applicant maintains that the amendments do not raise an issue of new matter. Support for the amendments can be found at least in the previous version of the claims. Entry of the amendments is respectfully requested.

Rejections under 35 U.S.C. §103(a)

1. Claims 49 and 50 stand rejected as being unpatentable over over Müller (Expert Opinion on Pharmacotherapy 3: 381-8, 2002) in view of Permax® prescribing information (2003).

2. Claims 54, 55, 92 and 93 stand rejected as being unpatentable over Müller in view of Silver et al. (Neurology Vol. 50, Suppl. 6, pp S18-22, 1998).

3. Claim 72 stands rejected as being unpatentable over Müller in view of Nystrom et al. (US 5,635,213).

Applicant respectfully traverses these rejections.

Applicant notes that in the previous Office Action, the Examiner rejected all claims ***solely*** for the fact that the claims allowed for "separate or sequential use" of pipamperone and the co-administered drug(s). No additional arguments for the rejection of the claims were provided. In reply thereto, all claims were amended by deleting the terms "separate or sequential." In the present Office Action, however, the Examiner reiterates the rejections of the previous Office Action even though applicant understands that the previous amendments should have obviated the previous rejections.

Combination of pipamperone and Parkinson's disease (PD) drugs

The present invention relates to the surprising finding that pipamperone ameliorates the effects of medicaments treating Parkinson's disease (PD), due to the dual high selective affinity of pipamperone, *i.e.* towards the serotonin **5-HT$_{2A}$** receptor as well as the Dopamine-4 (**D4**) receptor.

PD is linked to decreased dopamine production in the *substantia nigra*.

The most widely used form of PD treatment is L-dopa in various forms. L-dopa is transformed into dopamine in the dopaminergic neurons. Due to feedback inhibition, L-dopa results in a reduction in the endogenous formation of L-dopa. Moreover, L-dopa also results in desensitization of the dopamine receptors. Hence, L-dopa becomes counterproductive eventually. Another form of PD treatment is realized by dopamine agonists, such as bromocriptine, pergolide, pramipexole, etc., all of which are moderately effective. Dopamine agonists initially act by stimulating some of the dopamine receptors. However, they cause the dopamine receptors to become progressively less sensitive, thereby eventually increasing the symptoms. In addition, all dopamine agonists have their own side effects including somnolence, hallucinations and/or insomnia.

In addition, all contemporaneous anti-PD drugs induce side effects, particularly psychosis (see e.g. Meltzer et al. 1995 Neuropsychopharmacology 12:39-45, of record). Since this condition can be at least as disabling as the motor symptoms of PD, further intervention with antipsychotics is essential. The desired clinical effect of reducing psychotic symptoms is thought to be associated with blocking dopamine function in the ***mesolimbic pathway*** only. However, as many of the antipsychotics are not selective, they block dopamine in all pathways. When this happens in the ***nigrostriatal pathway***, similar movement problems to those found in PD occur (tardive dyskinesia). Indeed, although several atypical antipsychotic agents (e.g. clozapine and olanzapine) have been shown to be efficacious in reducing psychotic symptoms in PD, they either

require cumbersome monitoring, result in motor worsening or are associated with adverse effects, e.g. tolerability (see e.g. Marsh et al, 2000 Psychosomatics 41:15-23, attached in IDS). Hence, antipsychotics block D2 dopamine receptors in multiple pathways in the brain, counter-acting the PD treatment.

The non-response to dopamine receptor agonists in PD may be clarified by (partial) inhibition of dopamine release. The inventor hypothesized that serotonin inhibits dopamine release via 5-HT_{2A} receptor stimulation in the ***nigrostriatal*** dopaminergic neurons. Dis-inhibition thereof via 5-HT_{2A} antagonism seems to be the answer to this problem. However, not all compounds exhibiting 5-HT_{2A} antagonism are useful. Blocking of the 5-HT_{2A} receptor increases the dopamine release in the ***mesocortical cortex*** (which is apparently the goal of the treatment), but the increased dopamine concentration stimulates the D4 receptor as well. D4 receptor stimulation results in behavioral and cognitive impairment. Indeed, direct-acting dopamine agonists (*e.g.* ergoline derivates) are not very specific and interact with several subtypes of dopamine receptors, as well as with 5-HT receptors. In this respect, 5-HT and D4 stimulation may result in confusion, hallucinations and other psychiatric manifestations, such as psychosis. Dopamine agonists also act at the periphery, and this may contribute to significant side effects such as orthostatic hypotension and nausea.

Since pipamperone specifically blocks the D4 receptor, the side-effects of direct-acting dopamine agonists as well as other augmenting agents are forestalled.

Because of the need of specific **D4 antagonism** (leading to less extrapyramidal side-effects) and **5-HT_{2A} antagonism** in the treatment of PD with dopamine agonists and levodopa, pipamperone can be combined with such drugs, as pipamperone has less activity towards other receptors, especially the **D2 receptor** (needed to relieve the excessive burden of remaining dopaminergic neurons without being subject to metabolism into toxic free radicals inside dopaminergic neurons, as has been hypothesized for

levodopa). As such, drugs with a high affinity for the D2 receptor are highly contra-indicated. Indeed, pipamperone prevents induction of psychosis by contemporaneous anti-PD drugs. Hence, no atypical antipsychotics are required.

Pipamperone is contra-indicated in the prior art

As previously indicated, Applicant maintains that Müller teaches against combining pipamperone and PD drugs.

In addition, Applicant also maintains that Permax® also teaches against combining pipamperone with PD drugs: "Dopamine antagonists, such as ... butyrophenones (*e.g.* pipamperone) ... ordinarily should not be administered concurrently with Permax..." (page 1, right column, under "Drug Interactions, "(*e.g.* pipamperone)" added).

Moreover, Dipiperon prescription instructions also teach against the use of pipamperon with PD drugs: "The simultaneous use of ... anti-Parkinson medicines... increases the risk of tardive dyskinesia" and "It may be expected that antipsychotics block the function of dopamine-agonists, such as ... levodopa." (Dipiperon, page 4, attached in IDS).

In the field, it is indeed generally recognized that antipsychotics can cause Parkinsonism (*i.e.* Parkinson' disease-like symptoms, such as aggravation of motor symptoms), see also Müller.

Dose of pipamperone

The inventor surprisingly found that the ***dosage*** of active ingredient for pipamperone in the treatment could be ***very low*** compared to conventionally used dosages (which were used for the treatment of psychosis anyway).

The Dipiperon prescription information document states that an ***initial dose of 40 to 80 mg per day*** should be administered for 1 to 2 weeks. The optimal anti-

psychotic dose is reached after 3 to 6 weeks up to a maximum of 360 mg. It is further stated that it is recommended to ***increase the dose*** by 20 up to 120 mg per day. As such, Dipiperon teaches the skilled person to start with a low dose (which is still almost 3 to 8 times higher that the dosage in the present application), which is subsequently increased to an optimal, ***high*** dose. This is common practice to determine the optimal dosage for medicines, *i.e.* start low and build up, to ensure the lowest effective dose possible (in this respect, see also Silver, page 21, 1st line of Conclusions "start low, go slow").

Hence, Dipiperon teaches the skilled person that the starting dose should be 40 mg per day. The skilled artisan (also knowing that determining an optimal dose involves starting with a low, safe, and most of all non-optimal, even ineffective dose that can be increased over time) would therefore have no incentive to even further lower the dose than the minimal prescribed starting dose.

Müller relates to different matter

In the previous Office Action, the Examiner cites that

"It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose",

and

"It is obvious to combine two compositions taught by the prior art to be useful for the same purpose to form a third composition that is to be used for the very same purpose".

The present invention, however, does not relate to a combined composition for the very same purpose as described in the prior art.

In essence, Müller relates to the treatment of various Parkinson-***associated*** disorders or symptoms. These are merely disorders which exist on their own, but also can ***accompany*** PD. As such, all these disorders have their own causes, origins, etiology as well as method of treatment. One group of disorders mentioned in Müller is neuropsychiatric disturbances, such as depression and anxiety disorders, psychosis or dementia.

As such, Müller relates to the concomitant and individual treatment of these ***PD-associated disorders***. See also page 385, left column, of Müller, stating that "Treatment of additional concomitant infections or other general diseases, which may induce psychosis and/or delirium, is often necessary". Therefore, administration of pipamperone (which is contra-indicated anyway, see above) would have the specific purpose of treating psychosis as a PD-associated disorder, and not PD *per se*.

In this respect, the present invention in contrast relates to the treatment of PD *per se* and not to the treatment of PD-associated psychosis. See for instance paragraph [0066] on page 17 of the present application:

"According to a general aspect of the invention, it thus has been found by the present inventor that the compounds having a selective 5-HT2A and D4 antagonistic, inverse agonist or partial agonist activity as described above are useful for ***augmenting the therapeutic effect of another****, i.e. a second compound on a disease."* (emphasis added)

As such, pipamperone is administered to increase the effect of PD-drugs, *i.e.* preventing induction of psychosis, but not to treat PD-associated psychosis. In addition, as described above, the dose of pipamperone that is administered would be too low for the treatment of psychosis.

Therefore, Applicant maintains that Müller relates to different matter compared to the present invention, *i.e.* treatment of psychosis versus treatment of PD *per se*. In this context, if Müller is combined with either the Permax® prescription information, Silver,

or Nystrom, a person skilled in the art would still not end up at the present invention. Such a combination would teach a method for treating PD with pergolide (Permax®), levodopa/carbidopa (Silver), or levodopa/benserazide (Nystrom), wherein PD-associated psychosis might be treated with pipamperone.

Clinical examples

Clinical examples in related patent application family members (publication nos. 2005/0203130 and 2007/0078162) demonstrate that pipamperone at 5-15 mg per day ***in vitro as well as in vivo*** has a significant clinical effect on second compounds, which can be explained by the rationale as developed by the inventor. Pipamperone at 5-15 mg for instance blocks the **5-HT$_{2A}$** receptor and the **D4** receptor, because of which SSRIs, and SNRIs have an earlier onset and are more efficacious in various disorders.

Furthermore, results of these studies have been presented (Buntinx et al. POSTER attached) and published (Peremans et al. 2008 "Evaluation of serotonin-2A receptor occupancy with 123I-5-I-R91150 and single-photon emission tomography before and after low-dose pipamperone administration in the canine brain." Nucl Med Commun 29:724; attached).

Hence, the additional experimental results, including clinical data substantiate the observations by the inventor in that low amounts of pipamperone have indeed the clinical effect according to the proposed working mechanism.

Applicant respectfully maintains that the cited references do not render obvious the claimed invention. Accordingly, reconsideration and withdrawal of these rejections are respectfully requested.

Status of U.S. Patent Family Members

Applicant would like to advise the Examiner of the status of co-pending patent family members.

1. U.S. Patent Application No. 10/725,965. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on January 23, 2008, September 15, 2008, and June 10, 2009.

2. U.S. Patent Application No. 10/752,423. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on October 2, 2007, May 13, 2008, February 19, 2009, and August 5, 2009.

3. U.S. Patent Application No. 10/984,683. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on August 10, 2007, February 22, 2008, October 21, 2008, and July 21, 2009.

4. U.S. Patent Application No. 10/580,962. The claims have been subject to a restriction requirement. An Office Action on the merits of the application issued on June 2, 2009.

Supplemental Information Disclosure Statement

This Supplemental Information Disclosure Statement (SIDS) is being submitted pursuant to 37 C.F.R. §1.97(c)(2) to supplement the IDSs filed on November 7, 2008, April 4, 2008, August 21, 2007, April 11, 2007 and August 10, 2005 in connection with the subject application.

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the references that are listed on the attached forms PTO/SB/08A-B (3 pages). A copy of each non-U.S. patent documents is also attached.

CONCLUSIONS

Applicant respectfully requests that the Examiner reconsider and withdraw the rejections set forth in the February 20, 2009 Office Action, and earnestly solicits allowance of the claims under examination. If there are any minor matters preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

A check for $960.00 is enclosed for a small entity for the $555.00 fee for a three month extension of time and the $405.00 fee for filing a Request for Continued Examination (RCE). No other fee is deemed necessary in connection with the filing of this reply. However, if any other fee is required to maintain the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785. Please credit any overpayment to Deposit Account No. 01-1785.

Respectfully submitted,

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Dated: August 18, 2009
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By _____
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